NATIONAL INSTITUTE OF DENTAL RESEARCH

# NIDR Research Digest

JULY 1996

## Growth Factor Gene Linked to Human Dwarfism

A study at the NIDR has linked a mutation in a growth factor gene to a type of dwarfism that is characterized by abnormal development of the limbs and limb joints. The identification of the gene and its critical role in skeletal development could lead to new approaches for repairing cartilage and bone defects and reconstructing joints.

Scientists in the NIDR Bone Research Branch identified the structure of the human gene that carries the blueprint for a growth factor called cartilage-derived morphogenetic protein-1, or CDMP-1. The investigators discovered that a mutated version of the gene is present in individuals with a form of dwarfism known as Hunter-Thompson type chondrodysplasia. Affected individuals have shortened and misshapened bones in the lower arms and legs, with the most pronounced disturbances in the joints of the hands and feet. The fingers are very short and the toes are ball-shaped and functionless. The study results were reported in the March issue of *Nature Genetics*.

"The association of a CDMP-1 gene mutation with Hunter-Thompson chondrodysplasia provides direct evidence that this morphogenetic protein plays a key developmental role at sites of bone growth and joint formation," said Dr. Terrig Thomas, lead author on the paper.

Identification of the human gene opens the door for using recombinant DNA technology to produce CDMP-1 commercially and evaluate its potential for skeletal repair and joint reconstruction. Although the scientists still don't know exactly how the growth factor functions, recent work by study director Dr. Frank Luyten demonstrated that a recombinant form of CDMP-1 led to the formation of cartilage and bone when implanted under the skin of rats.

### Studies Provide Clues

The discovery of the human gene mutation evolved from recent findings in several laboratories. A mouse strain with short and deformed limbs was found to be caused by a mutation in the mouse equivalent of the CDMP-1. Meanwhile, Dr. Luyten and

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## NIDR Featured on "Dental Health Check"

Dr. Linda Niessen of the Baylor College of Dentistry (center) and cameraman Patrick Broyles listen to a patient with a temporomandibular disorder describe her experience. Dr. Niessen and her crew spent two days in June at the NIDR filming stories and conducting interviews for "Dental Health Check," a series of television segments on oral health research and practice for the consumer. The segments air weekly on network affiliates in Seattle, New Orleans, and northern Texas.

Other topics covered by Dr. Niessen during her visit to the NIDR included gene therapy for salivary gland disorders, genetic studies of cleft lip and palate, PET scan imaging of pain, dental implants in children with ectodermal dysplasia, and a salivary protein that blocks HIV infection. ■

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colleagues at NIH demonstrated that the human gene for CDMP-1 becomes active during fetal development, and is switched on primarily in the cartilaginous portions of developing limb bones and joints. “The Hunter-Thompson cases reported in the literature had abnormalities in the same areas of the body in which we observed CDMP-1 gene activity, ” said Dr. Luyten. “Coupled with the mouse data, this human disorder became a prime candidate for a defect in CDMP-1.”

The investigators determined the DNA sequence of the CDMP-1 gene and found an extra piece of DNA inserted into the gene of those affected with Hunter-Thompson chondrodysplasia. According to Dr. Luyten and Dr. Thomas, the mutation most likely results in a faulty protein that can’t carry out its role in the normal development of limbs and joints.

CDMP-1 is a growth regulator that is a member of the transforming growth factor-beta (TGF-beta) superfamily of proteins, which have many diverse functions in normal development across the animal kingdom. Despite the fact that Hunter-Thompson chondrodysplasia is quite rare and has been documented only in a few families from isolated communities, this study is the first example of a human disorder attributable to a mutation in one of these proteins.

The investigators on this study were Drs. J. Terrig Thomas, Keming Lin, Maithily Nandedkar, and Frank Luyten of the NIDR Bone Research Branch; Dr. Mauricio Camargo of the University of Antioquia, Medellin, Columbia; and Dr. Jaroslav Cervenka of the University of Minnesota School of Dentistry. Blood samples from affected individuals and their families, obtained in collaboration with scientists from Medellin, Columbia, were used to isolate the DNA. ■

*—Wayne Little*

# NIH Panel Makes Recommendations For Temporomandibular Disorders

An independent panel convened by the National Institutes of Health recommended a conservative and reversible approach to treatment for the vast majority of patients with temporomandibular disorders (TMD).

“The absence of reliable scientific data has led to confusion among dentists and physicians regarding when and how to treat TMD,” said panel chair Judith E. N. Albino, Ph.D., president emerita and professor of psychiatry at the University of Colorado Health Science Center in Denver. “The good news, however, is that for most people initial TMD pain is not a signal that a serious problem is developing. Only a small percentage will develop significant, long-term symptoms,” she said.

The panel estimated that more than 10 million Americans have symptoms associated with TMD, which is most often seen in women 20 to 40 years of age.

## Reversible Treatment Options

TMD treatment falls into two main categories: conservative/reversible and irreversible. Conservative treatments do not invade the tissues of the face, jaw, or joint. These treatments are as simple as possible and are used most often because most patients do not have severe, degenerative TMD. Conservative approaches include self-care practices such as eating soft foods, applying heat or ice packs, and avoiding extreme jaw movements like wide yawning, singing, and gum chewing. Learning special techniques for relaxing and reducing stress may also help patients deal with pain that often comes with TMD problems. Other conservative therapies may include education, pain control medication, and physical therapy. Reversible treatments do not cause permanent changes in the structure or position of the jaw or teeth.

## Irreversible Treatments

Irreversible treatments for TMD, which include surgical procedures, result in permanent alterations to the jaw joint or teeth. The panel emphasized that surgical treatments are only indicated in a small percentage of patients. When such treatment is necessary, however, it is essential the patient fully understand the reason for the treatment, the risks involved, and other types of treatment that may be available. For patients who have already undergone surgery, additional operations should be considered only with great caution, as the probability of success decreases with each additional intervention.

A form of occlusal adjustment irreversibly alters tooth structure by grinding down teeth to bring the bite into balance. The panel noted that there are no clinical trials demonstrating that this treatment is superior to noninvasive therapies. They recommended that more research is needed to clarify the role of occlusal adjustment in the management of TMD.

## Diagnostic Problems

TMD has been used to characterize individuals with a wide variety of symptoms and signs, such as pain in the face or jaw joint area; headaches, earaches, and dizziness; clicking sounds in the jaw joint; or locking of the jaw. The severity of these symptoms may range from painless clicking to serious debilitating pain and dysfunction.

The 15-member panel noted that there are significant problems with some of the present diagnostic categories for TMD, since they appear to be based on signs and symptoms rather than cause and epidemiological information. The panel called for carefully designed population studies to identify the prevalence of TMD signs and symptoms as a basis for the development of a more precise classification system. Such a system could lead to new diagnostic techniques to identify disease subtypes. These new, more specific disease categories could permit the elimination of the term "TMD," which has become emotionally laden and contentious.

The panel noted that universally accepted, scientifically based guidelines for diagnosing and managing TMD are not available and that consequently practitioners sometimes have attempted to respond to their patients' needs with a variety of unproven diagnostic and therapeutic approaches. Concerns about the safety and effectiveness of these approaches, as well as the potential for harm, led the panel to recommend studies to assess the accuracy, reliability, and cost-effectiveness of currently used diagnostic tools.

## Need for Clinical Trials

The panel concluded that there are questions about the effectiveness of most treatments now used for TMD. Most have not been adequately evaluated in long-term studies and virtually none in randomized clinical trials. The group called for clinical trials on the efficacy of non-invasive therapy versus placebo and research on the self-management of TMD signs and symptoms. In addition, the panel strongly encouraged professional education to insure proper and safe practice in the treatment of TMD, particularly with regard to medications, surgery, and understanding the psychological and social aspects of these TMD symptoms. The panel pointed optimistically to new research developments in tissue engineering and microbiology, which promise exciting advances in the future management of TMD.

The panel made their recommendations at the conclusion of the 3-day NIH Technology Assessment Conference on Management of Temporomandibular Disorders. The conference was convened April 29-May 1 by the NIDR and the NIH Office of Medical Applications of Research. It was cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute of Nursing Research, and the NIH Office of Research on Women's Health.

## Summary Statement

Free copies of the summary statement from the TMD conference are available from: NIH Consensus Program Information Center, P.O. Box 2577, Kensington, MD 20891. Telephone: 1/888-644-2667; Internet: http://www.nih.gov (select "HEALTH INFORMATION") ■

*—Patricia Sheridan and Bill Hall*

# Large Scale Study Looks at Link Between Periodontal and Heart Disease

A 4-year, $2.2 million grant has been awarded to the University of North Carolina (UNC) by the NIDR to better define the link between periodontal disease and heart disease. This is the largest study of its kind enabling researchers to explore in detail the underlying inflammatory responses common to both diseases.

By tapping into the ongoing Atherosclerosis Risk in Communities Study (ARIC) sponsored by the National Heart, Lung and Blood Institute, UNC researchers will be able to examine markers of periodontal disease in 14,000 individuals already receiving extensive heart disease testing through the ARIC study. The dental researchers will then compare these periodontal markers with clinical measures of heart disease; the occurrence of heart attacks, stroke, and death; and ultrasound measures of carotid vessel thickening. The researchers hope that these comparisons will uncover the biological association between dental disease and heart disease.

## Bacteria Implicated

Several previous studies, including smaller ones conducted by the UNC researchers, have shown that individuals with severe periodontal disease are more likely to develop heart disease than are people without gum problems. One study even suggested that individuals with severe periodontal bone loss may have twice the risk of fatal coronary heart disease as normal individuals, after controlling for other relevant risk factors.

Part of the link between periodontal disease and heart disease may lie with harmful bacteria that colonize the mouth. The investigators theorize that certain types of these bacteria that cause periodontal diseases also activate white blood cells in the body to release harmful clotting factors and proteins (called pro-inflammatory mediators) that contribute to heart disease and stroke.

"Establishing periodontal diseases as a risk factor for heart disease and stroke would take on new meaning for oral health as it relates to the overall health of individuals," accord-

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ing to Drs. James D. Beck and Steven Offenbacher, principal and co-principal investigators of the study. Dr. Beck is the Kenan professor and chair of the Department of Dental Ecology at the UNC School of Dentistry; Dr. Offenbacher is a professor of periodontology at the UNC School of Dentistry and a member of the graduate faculty.

### Comparison of Disease Markers

The UNC researchers will look at several measures of periodontal disease and biological responses in ARIC study participants. First, they will measure participants' periodontal pocket depth and attachment loss. The researchers also will collect samples of gingival crevicular fluid to see if it contains the same inflammation-provoking substances associated with heart disease. Finally, blood samples will be collected to be analyzed later for antibodies to periodontal bacteria.

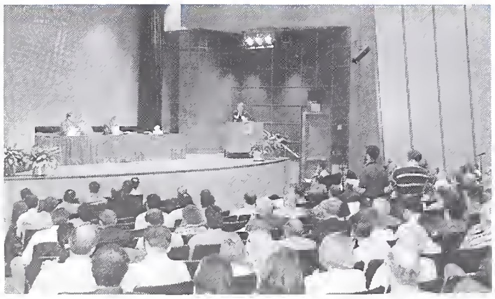
With this information in hand, the researchers will compare these periodontal measures and responses to known risk factors for heart disease, such as elevated lipid levels in the blood and clotting factors. They will determine whether severe narrowing of the arteries, as well as elevated lipid levels and clotting factors, are associated with high levels of pro-inflammatory mediators in gingival crevicular fluid.

Participants in the periodontal/heart disease study reside in four communities: Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD. They range in age from 45-64 years and are of various ethnic backgrounds.

Working with Drs. Beck and Offenbacher on the periodontal part of the study at UNC are Drs. Gerardo Heiss, Herman Tyroler and Gary Koch from the UNC School of Public Health, and Frances Smith, from the UNC Dental Research Center. The following institutions are also collaborating with UNC on the study: Wake Forest University; the Bowman Gray School of Medicine, Public Health Science; the University of Minnesota School of Public Health, Division of Epidemiology; the University of Mississippi Medical Center, Department of Medicine; and The Johns Hopkins School of Hygiene and Public Health. ■

*—Jody Dove*

# NIDR Hosts Successful Scientific Frontiers Symposium



More than 500 participants attended the "Scientific Frontiers in Clinical Dentistry" symposium for dental practitioners, held June 13-14 on the NIH campus. This was the fifth such symposium sponsored by the NIDR since 1991. The symposium featured experts who discussed promising new areas of fundamental and applied research and their impact on the future practice of dentistry.

Members of the panel on "Changing Paradigms" (pictured l. to r.)—Dr. Kenneth J. Anusavice, University of Florida; Dr. Harold Slavkin, NIDR director; and Dr. Kenneth Kornman, University of Texas Health Science Center at San Antonio—respond to questions from the audience about breaking tradition in preventive and restorative care and the practice of dentistry in the 21st century.

Representing the organizations that sponsored "Scientific Frontiers" were (l. to r.): Dr. Victor A. Sandoval, president, American Association of Dental Schools; Dr. Robert J. Collins, deputy executive director, American/International Association for Dental Research; Dr. Sherry Keramidas, executive director, American College of Dentists; Dr. Harold C. Slavkin, director, NIDR; and Dr. John S. Zapp, executive director, American Dental Association.

The *NIDR Research Digest* is published periodically by the National Institute of Dental Research. Its purpose is to communicate NIDR research findings and other activities of interest to those working in the field of dental research.

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